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(54) Title: METHOD FOR THE MANUFACTURE OF ANAGRELIDE

(57) Abstract: Methods are provided for making certain 6,7-dihaol-1,5-dihydroimidazo [2,1-b]quinazolin-2(3H)-ones from 2,3-dihalobenzaldehydes. A method is also provided for making the intermediate ethyl N-(2,3-dihalo-6-nitrobenzyl)glycines from 2,3-dihalobenzaldehydes and for reducing the glycine compounds using either $SnCl_2$ or a specially defined catalyst. A cyclization method to form the desired 6,7-dihalo-1,5-dihydroimidazo[2,1-b]quinazolin-2(3H)-ones from the corresponding iminquinazoline compounds is further provided. These methods are particularly suitable in the manufacture of Anagrelide base.

METHOD FOR THE MANUFACTURE OF ANAGRELIDE

Background Of The Invention

1. Field of the Invention

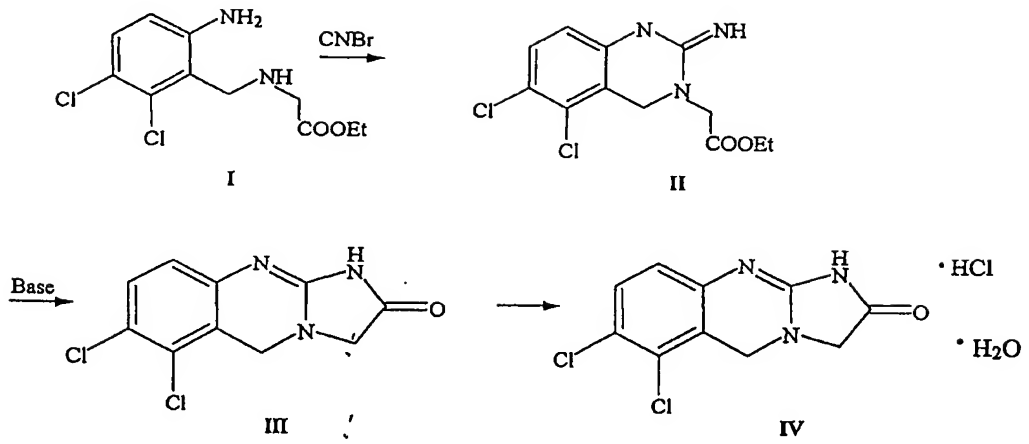
The invention relates to 6,7-dichloro-1,5-dihydroimidazo[2,1-b]quinazolin-2(3H)-one (compound III), more commonly known as Anagrelide base and, more particularly, to a method for the manufacture of Anagrelide base.

2. Description of Related Art

Anagrelide (6,7-dichloro-1,5-dihydroimidazo[2,1-b]quinazolin-2(3H)-one, (compound III) is a potent blood platelet reducing agent. A number of U.S. Patents have issued on Anagrelide and its method of making including Nos. 3,932,407; 4,146,718; 4,208,521; 4,357,330; Re 31,617; and 5,801,245. These patents are incorporated herein by reference.

Commercially, as discussed in U.S. Patent No. 5,801,245 and as shown in Figure 1, Anagrelide has been prepared as the hydrochloride monohydrate (compound IV) from the intermediate, ethyl N-(6-amino-2,3-dichlorobenzyl)glycine (compound I) by reaction with cyanogen bromide in hot alcohol solution, or, preferentially, by reaction with cyanogen bromide in an aprotic solvent to give the iminoquinazoline intermediate (compound II) which is isolated and then reacted with a base in a hot solution of alcohol to form Anagrelide base (compound III).

Figure 1



The hydrochloride monohydrate Anagrelide salt (compound IV) is prepared by adding hydrochloric acid to a methanol slurry of Anagrelide base (compound III) and heating to reflux. The hydrochloride salt is then hydrated in a high humidity chamber. These two steps are time-consuming however, and the yield of hydrochloride salt can be poor due to competing acid hydrolysis of the lactam ring and methyl ester formation. After 15 minutes at reflux, the isolated yield is 62% and this decreases to 40% after 2 hours.

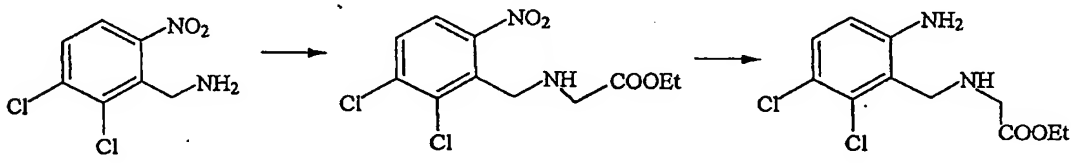
Normally, salts are prepared when the free base has undesirable properties such as poor solubility or a non-solid physical state. In this case, both Anagrelide base (compound III) and the hydrochloride salt (compound IV) are solids with low aqueous solubility. In addition, the water of crystallization can accelerate decomposition of the parent molecule through hydrolysis of the lactam ring and this presents long-term stability problems for pharmaceutical Anagrelide formulations.

Radiolabeled Anagrelide base has been used in pharmacokinetic studies in humans and monkeys and results show complete absorption into blood plasma demonstrating that the base is bioavailable. The free-base is converted into the hydrochloride salt in the stomach to enhance absorption. Both the salt and the

base exhibit equivalent pharmacological effects, and there is no inherent advantage to using the hydrochloride monohydrate salt as the active pharmaceutical agent.

As an important intermediate in the synthesis of Anagrelide, ethyl N-(6-amino-2,3-dichlorobenzyl)glycine (compound I) has been prepared from 2,3-dichloro-6-nitrobenzylamine (compound V) as shown in Figure 2. This material is no longer commercially readily available, however, as the precursor 2,3-dichloro-6-nitrobenzonitrile has extreme toxic and skin-irritant properties.

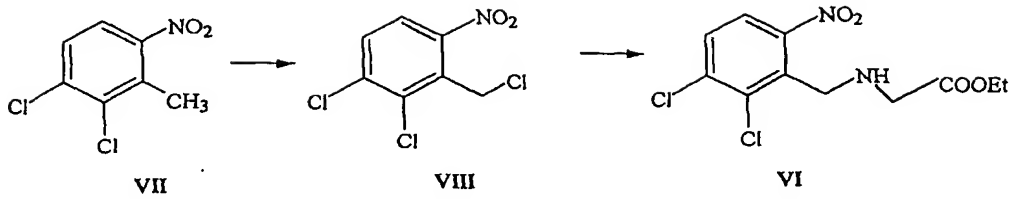
Figure 2



The conventional process for the formation of ethyl N-(6-amino-2,3-dichlorobenzyl)glycine (compound I) from 1,2,3-trichlorobenzene is shown in U.S. Patent No. 4,146,718.

An improved process for the formation of ethyl-N-(6-amino-2,3-dichlorobenzyl)glycine (compound I) involving the intermediate 2,3-dichloro-6-nitrobenzyl halide (compound VIII), where halide is iodide, chloride or bromide, has been developed as an environmentally acceptable alternative (Figure 3). The route of preparation from 2,3-dichloro-6-nitro-toluene (compound VII) is claimed in U.S. Patent No. 5,801,245, and involves a radical halogenation of the toluene group. Radical conditions can be nonselective, however, and could be difficult to effectively implement in large-scale commercial manufacture.

Figure 3



In both reactions shown in Figs. 2 and 3, ethyl N-(2,3-dichloro-6-nitrobenzyl)glycine (compound VI) is reduced to the 6-amino-2,3-dichlorobenzyl glycine (compound I) by stannous chloride reduction ($SnCl_2$/HCl). A disadvantage of this route is the formation of large amounts of tin-containing waste products. In addition, the strongly acidic reaction conditions can promote chlorination of the aromatic ring, producing a mixture of tri-chloro impurities which are difficult to remove in successive steps.

Bearing in mind the problems and deficiencies of the prior art, it is therefore an object of the present invention to provide a method for the making of Anagrelide HCl (compound IV) and Anagrelide base (compound III).

It is an additional method of the present invention to make intermediate 2,3-dichloro-6-nitrobenzyl chloride (compound VIII) from readily available starting materials.

It is another object of the present invention to provide a method for making intermediate ethyl-(6-amino-2,3-dichlorobenzyl)glycine (compound I) from ethyl N-(2,3-dichloro-6-nitrobenzyl)glycine (compound VI) using either $SnCl_2$ or a hydrogenation catalyst as the reducing agent.

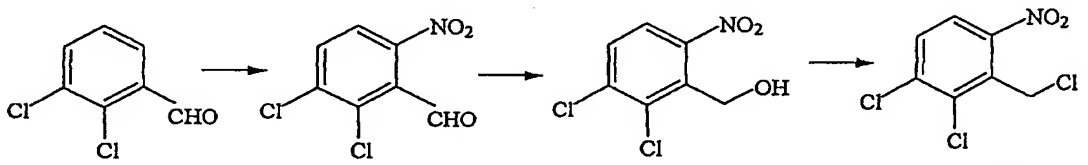
A further object of the present invention is to provide a method for the cyclization of 5,6-dichloro-3,4-dihydro-2(1H)iminoquinazoline-3-acetate HBR (compound II) to form Anagrelide base (compound III).

Still other objects and advantages of the present invention will in part be obvious and will in part be apparent from the specification.

Summary of the Invention

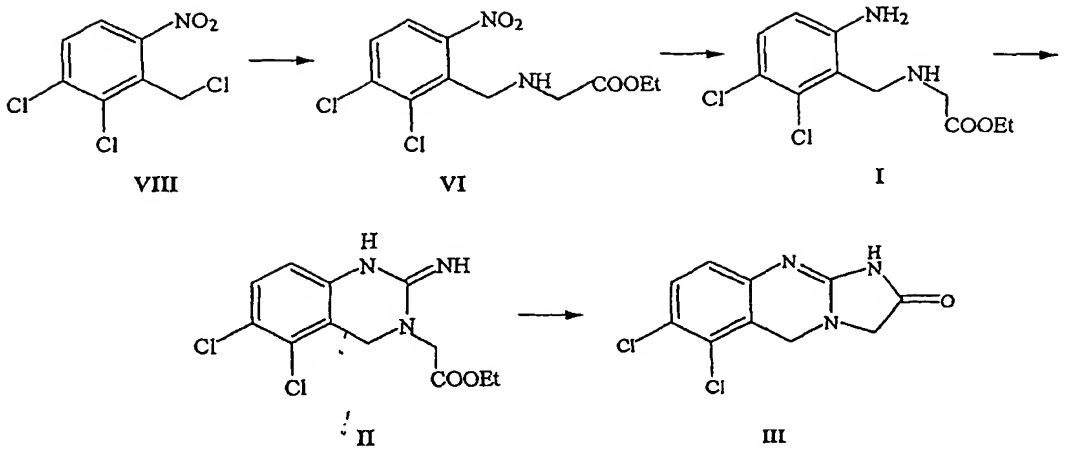
The above and other objects, which will be apparent to those skilled in the art, are achieved by the present invention which relates in a first aspect to an environmentally acceptable method for making the intermediate 2,3-dichloro-6-nitrobenzyl chloride (compound VIII) from readily available starting materials (Figure 4). As shown in Figure 4, 2,3-dichlorobenzaldehyde (compound IX) is nitrated preferentially at the 6-position to form 2,3-dichloro-6-nitro benzaldehyde (compound X), separated from its isomer, and reduced to 2,3-dichloro-6-nitrobenzyl alcohol (compound XI) under standard hydride conditions. Treatment of the alcohol under standard nucleophilic displacement conditions gives 2,3-dichloro-6-nitrobenzyl chloride (compound VIII).

Figure 4



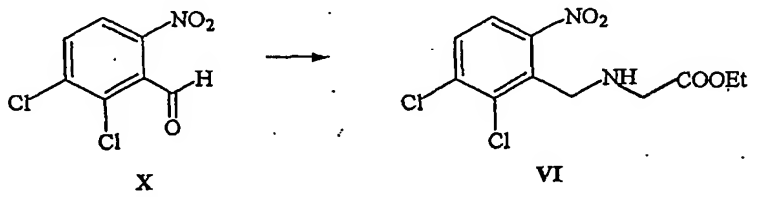
The above compounds can also contain substituents such as F,Cl, Br and I and the like. Further, the 2,3 chlorine atoms may likewise be substituted with substituents such as F, Br and I. This will also apply to the other reaction schemes shown hereinbelow and for convenience the description will be directed to the desired unsubstituted dichloro compounds.

Ethyl N-(2,3-dichloro-6-nitrobenzyl)glycine (compound VI) is then produced by reaction of 2,3-dichloro-6-nitrobenzyl chloride (compound VIII) with ethyl glycine, compound VI reduced to form compound I which is reacted to form compound II and then cyclized to form Anagrelide base (compound III) as shown below:



Alternatively, compound VI can be made directly from 2,3-dichloro-6-nitro benzaldehyde (compound X) by reductive amination with a glycine ester as shown in Figure 5. This is a novel approach to the known intermediate compound VI, which intermediate is reduced to compound I by either catalytic hydrogenation or by stannous chloride preferably following the method of the invention.

Figure 5



Normally, catalytic hydrogenation of aromatic chloro compounds such as ethyl N-(2,3-dichloro-6-nitrobenzyl)glycine (compound VI) is accompanied by excessive dechlorination, however, it has been found that a specially defined poisoned catalyst (for example, sulfided platinum on a carbon support) allows the selective reduction of the nitro group without significant chlorine loss at moderate hydrogen pressures. Other catalysts include Raney nikel, rhodium or palladium on a carbon support. This is an environmentally acceptable alternative to the tin-acid reductions conventionally used in the preparation of Anagrelide since the

heterogeneous poisoned catalyst can be recycled. This novel method eliminates the production of large quantities of tin-containing waste of the prior art and produces material in higher yield and purity than the conventional route. Though this selective catalytic hydrogenation is preferable, this invention also includes, in another aspect an improved reduction reaction under stannous chloride/acid conditions that allows control of trichloro impurities.

Another aspect of the invention for the preparation of Anagrelide is the discovery that the final cyclization reaction as shown for example in Figure 1 to form 6,7-dichloro-1,5-dihydroimidazo[2,1-b]quinazoline-2(3H)one (compound III) from 5,6-dichloro-3,4-dihydro-2(1H)iminoquinazoline-3-acetate HBR (compound II) can be achieved at room temperature by addition of an organic base such as triethylamine (TEA), pyridine, or trimethylamine, preferably TEA, to a suspension of the starting material in water. Anagrelide base is obtained in about 99.8 % purity by HPLC. The preparation of Anagrelide base from ethyl 5,6-dichloro-3,4-dihydro-2(1H)iminoquinazoline-3-acetate hydrobromide (compound II) is conventionally achieved by cyclization in refluxing organic alcohols in the presence of a base. This leads to occlusion of residual solvents or organic impurities in the final product. Due to the low solubility of Anagrelide free base in most organic solvents, further purification at this stage is limited. Since the iminoquinazoline intermediate 5,6-dichloro-3,4-dihydro-2(1H)iminoquinazoline-3-acetate HBR (compound II) is insoluble in water at room temperature, the discovery that this media affords much purer Anagrelide base (compound III) is surprising and novel.

The formation of the Anagrelide hydrochloride salt in refluxing methanol/hydrochloric acid possesses a powerful purification effect, readily removing the organic and solvent impurities. However, at reflux conditions, acid hydrolysis is fast and the yield of hydrochloride salt decreases rapidly over time. With the larger batch sizes needed for commercial manufacture, the time the reaction mixture spends at reflux is significant. Thus, formation of the hydrochloride salt is a less efficient means of purification than preparing Anagrelide base (compound III) in high purity using the method of the invention.

Description of the Preferred Embodiments

The nitration of 2,3-dichlorobenzaldehyde (compound IX) to form 2,3-dichloro-6-nitro benzaldehyde (compound X) is performed preferably by adding concentrated nitric acid to a solution of compound IX in sulfuric acid using an ice bath to maintain a reaction temperature of about -10 to 40°C, preferably 20-25°C. The reaction mixture is generally stirred at this temperature for one hour or more and then preferably suspended in water and filtered. The filter cake is preferably washed with water to give a mixture of the compound X and its isomer 5-nitrobenzaldehyde. The isomers may be separated using an organic solvent such as hexane until the 5-nitro isomer is removed.

To form 2,3dichloro-6-nitro benzylalcohol (compound XI) from 2,3-dichloro-6-nitro benzaldehyde (compound X), compound X is preferably solubilized in a solvent such as toluene and methanol. The solution of compound X is added to a reducing solution such as sodium borohydride in an organic solvent over a period of time to maintain a reaction temperature below about 40°C, preferably 25°C. The reaction is preferably stirred for 24 hours at room temperature under nitrogen and then washed with water. After removing the aqueous layer the organic layer is azeotropically dried and concentrated forming 2,3dichloro-6-nitro benzylalcohol (compound XI).

To form 2,3-dichloro-6-nitrobenzyl chloride (compound VIII) from 2,3dichloro-6-nitro benzylalcohol (compound XI) a concentrated solution of compound XI is preferably prepared and a base such as triethylamine is added to the concentrated solution. To this solution is added a chlorinating material, preferably thionyl chloride, over about 15 minutes. Following addition, the solution is heated for a number of hours such as 45-50°C for 18 hours and then cooled to room temperature. Water and organic solvents such as toluene are added to the reaction mixture and the mixture filtered. The organic layer is washed with water and dried by azeotropic distillation and the solution concentrated to give 2,3-dichloro-6-nitrobenzyl chloride (compound VIII).

Ethyl N-(2,3-dichloro-6-nitrobenzyl)glycine (compound VI) is formed from 2,3-dichloro-6-nitrobenzyl chloride (compound VIII) by preferably reacting under nitrogen an organic base such as triethylamine, a glycine ethylester and a phase transfer castalyst such as cetyltrimethyl ammonium bromide at an elevated temperature such as 80°C for 24 hours. To the cooled mixture is added a salt solution such as sodium chloride and the organic phase separated, washed with water and concentrated. The salt ethyl N-(2,3-dichloro-6-nitrobenzyl)glycine (compound VI) is prepared by treating the crude material with HCl and isopropanol and filtering the precipitate.

Ethyl N-(2,3-dichloro-6-nitrobenzyl)glycine (compound VI) is preferably prepared by reductive amination of 2,3-dichloro-6-nitrobenzaldehyde (compound X) with a mixture of TEA and an alcohol. A reducing agent such as sodium cyanoborohydride is added in small portions and reaction mixture stirred. The product is isolated by filtration.

Ethyl-(6-amino-2,3-dichlorobenzyl)glycine (compound I) is preferably prepared from ethyl N-(2,3-dichloro-6-nitrobenzyl)glycine (compound VI) using a mixture of stannous chloride and hydrochloric acid following the method of the invention. A solution of ethyl N-(2,3-dichloro-6-nitrobenzyl)glycine (compound VI) is slowly added to the tin solution and the resulting reaction mixture heated at an elevated temperature of about 40-50°C for about two hours. Solids are filtered and the filtered cake dissolved in water and an organic solvent such as methylene chloride. The pH of the solution is adjusted to about 12.5 with sodium hydroxide and the organic phase separated and the aqueous phase extracted with methylene chloride. The combined organic phases are washed with water and dried azeotropically and the solution is concentrated, an organic solvent added and the solution cooled to -20 to -30°C. The precipitated solids are collected by filtration and the crude product is recrystallized from heptane or another organic solvent.

Ethyl N-(2,3-dichloro-6-nitrobenzyl)glycine (compound VI) may also be catalytically hydrogenated using a sulfided platinum on carbon catalyst under hydrogen pressure. The catalyst is then removed by filtration and the filtrate

concentrated, diluted with water and an organic solvent and basified using an alkali to a pH of about 9-10. The organic phase is separated and concentrated and the crude material purified by low temperature recrystallization to give ethyl-(6-amino-2,3-dichlorobenzyl)glycine (compound I).

6,7-dichloro-1,5-dihydroimidazo[2,1-b]quinazoline-2(3H)one (compound III) may be prepared from compound II by suspending 5,6-dichloro-3,4-dihydro-2(1H)iminoquinazoline-3-acetate HBR (compound II) in water and adding an organic base such as TEA. After filtering the solution the filtered cake is washed in water and the solids suspended in alcohol. After filtering, the solids are rinsed in an alcohol and dried to give compound III.

Examples

Preparation of 2,3-Dichloro-6-nitrobenzaldehyde (X)

A solution of 40 g of 2,3-dichlorobenzaldehyde (compound IX) in 160 mL of concentrated sulfuric acid (95-98% w/w) is heated to 40°C and stirred to form a solution, then cooled to 20-25°C. Concentrated nitric acid (69-71% w/w; 24.7g) is added to this solution over 20 minutes (an ice bath is used to maintain a reaction temperature of 20-30°C). The reaction mixture is stirred at room temperature for 1 hour, and then added in portions to 600 mL of water. The resulting suspension is stirred for 2 hours and filtered. The filter cake is washed (3 x 50 mL of water). The filter cake is agitated with 200 mL of water for 2 hours and filtered. The filter cake is washed (3 x 50 mL of water) and dried *in vacuo* to give a mixture of the compound X and the isomer, 2,3-dichloro-5-nitrobenzaldehyde.

The crude product is triturated with hexanes for 3 hours and filtered. The filter cake is washed with hexanes (2 x 70 mL). This trituration procedure is repeated with fresh hexanes until the 5-nitro isomer is removed. The filter cake is then dried *in vacuo* to give the purified compound X in 44 to 50% yield.

^{1}H NMR($CDCl_3$, 300MHz): δ 7.8(d, 1H); 8.0 (d, 1H); 10.4 (s, 1H)

Preparation of 2,3-Dichloro-6-nitrobenzylalcohol (XI)

A solution of 40 g of 2,3-dichloro-6-nitrobenzaldehyde (compound X) in 200 mL of toluene was stirred for five minutes. Then, 7.4 mL of methanol was added and mixing continued until all the solids had dissolved. Separately, a solution of 2.41 g of sodium borohydride in 120 mL of toluene was prepared. The benzaldehyde solution was added by drops to the borohydride solution over 20 minutes to maintain the reaction temperature below 25°C. The reaction mixture was stirred for 24 hours at room temperature under nitrogen. Forty mL of water was added and the mixture stirred for 15 minutes. The aqueous layer was removed and the organic layer washed with water (3 x 40 mL). The organic layer was azeotropically dried using a Dean-Stark trap, and concentrated to 280 mL. The 2,3-dichloro-6-nitrobenzylalcohol (compound XI) was used without further purification.

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.8 (d, 1H); 7.6 (d, 1H); 5.0 (s, 2H)

Preparation of 2,3-dichloro-6- nitrobenzyl chloride (VIII)

Under nitrogen, 27.9 mL of triethylamine was added to the concentrated solution of 2,3-dichloro-6-nitrobenzylalcohol (compound XI) prepared in the previous step. To this solution, 14.6 mL of thionyl chloride was added via an addition funnel over 15 minutes. Following addition, the solution is heated to 45-50°C for 18 hours, then cooled to room temperature under nitrogen. Water and toluene are added to the reaction mixture and the mixture filtered. The filtrate is diluted with water, and the aqueous layer removed. The organic layer is washed with water (4 x 40 mL), and dried by azeotropic distillation. The solution is concentrated to give 1,2-dichloro-3-chloromethyl-4-nitrobenzene (compound VIII), which could be used without further purification.

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.8 (d, 1H); 7.6 (d, 1H); 5.0 (s, 2H)

Preparation of Ethyl N-(2,3-dichloro-6-nitrobenzyl)glycine hydrochloride (VI)

A. Alkylation

Under nitrogen, 47.5 mL of triethylamine, 25.9 g of glycine ethyl ester hydrochloride and 2.8 g of cetyltrimethylammonium bromide is added to the toluene solution of 1,2-dichloro-3-chloromethyl-4-nitrobenzene (compound VIII) prepared in the previous step. The reaction mixture is heated at 80°C for 24 hours. To the cooled mixture is added 40 mL of 20% NaCl solution. The organic phase is separated, washed with water, and concentrated. The salt (compound VI) is prepared in 66 to 71% yield by treating the crude material with HCl in isopropanol and filtering the precipitate.

B. Reductive Amination

The compound (VI) can be prepared by reductive amination of 2,3-dichloro-6-nitrobenzaldehyde (compound X) with 1.1 equivalents of glycine ethyl ester hydrochloride in a mixture of anhydrous triethylamine over KOH and 95:5% mixture of ethanol and isopropanol. Sodium cyanoborohydride (2.5 equivalents) is added in small portions and the reaction mixture stirred for 16 hours. The product is isolated by filtration. The filtrate is concentrated, dissolved in ethyl acetate and washed with saturated aqueous sodium chloride solution. The organic base is extracted (2 N HCl,4x), the aqueous phases combined and neutralized with saturated aqueous potassium carbonate. The aqueous phase is next extracted with ethyl acetate. The organic phases are combined, washed with saturated aqueous sodium chloride solution, dried (sodium sulfate) and concentrated to give the product in 60% yield.

^{1}H NMR (300 MHz, DMSO-d_6): δ 9.89 (br s, NH); 8.23 (d, 1H, J = 9.2 Hz, C(2)-H); 8.08 (d, 1H, J = 8.8 Hz, C(3)-H); 4.69 (s, 2H, C(7)-H_2); 4.23 (q, J = 7 Hz, 2H, C(10)-H_2); 4.12 (s, 2H, C(8)-H_2); 1.26 (t, J = 7 Hz, 3H, CH_3)

^{13}C NMR (75 MHz, DMSO-d_6): δ 13.90 (C11); 44.86 (C7); 47.74 (C8); 125.06 (C2); 127.72 (C6); 132.90 (C3); 135.65 (C5); 137.99 (C4); 149.11 (C1); 166.43 (C9)

UV: 214 nm (Σ = 18447 $M^{-1}cm^{-1}$); 266 nm (Σ = 7054 $M^{-1}cm^{-1}$); 328 nm (Σ = 1593 $M^{-1}cm^{-1}$)

MS: 307 (M^+)

IR (KBr dispersion): 1750 cm^{-1} (C=O); 1520 (NO_2); 1350 (NO_2) 1210 (C-O); 875 (C-N)

Preparation of Ethyl N-(6-amino-2,3-dichlorobenzyl)glycine (I)

A. $SnCl_2$ Reduction

A suspension of 30 g of ethyl N-(2,3-dichloro-6-nitrobenzyl)glycine hydrochloride (compound VI) in 120 mL of concentrated hydrochloric acid was prepared. Separately, a mixture of tin chloride dihydrate (88.6 g) in 60 mL of hydrochloric acid is prepared. The glycine solution is slowly added to the tin solution and the resulting reaction mixture heated for 2 hours at 40-50°C. The solids are filtered, and the filter cake dissolved in water and methylene chloride. The pH of this solution is adjusted to 12.5 with 50% NaOH. The organic phase is separated and the aqueous phase extracted with methylene chloride. The combined organic phases are washed with water, and dried azeotropically. The solution is concentrated, isopropanol and heptane are added, and the solution cooled to -20 to -30°C. The precipated solids are collected by filtration. The crude product is recrystallized from heptane to give compound I in 58 to 67% yield.

B. Catalytic hydrogenation

A solution of 0.344 g of ethyl N-(2,3-dichloro-6-nitrobenzyl)glycine hydrochloride (compound VI) in 1.5 mL of water and 1.5 mL ethanol (with 5% isopropanol) was stirred and 5% sulfided platinum on carbon under hydrogen (50 to 100 psi) for 16 hours. The catalyst was removed by filtration. The filtrate concentrated, diluted with water and toluene, and basified (aqueous sodium hydroxide or potassium carbonate) to pH 9-10. The organic phase was separated, concentrated, and the crude material purified by low-temperature recrystallization from toluene in hexane to give compound I in 72% yield.

^{1}H NMR (300 MHz, DMSO-d_6): δ 7.18 (d, 1H, J = 8.8 Hz); 6.64 (d, 1H, J = 8.8 Hz); 5.74 (s, 2H); 4.11 (q, 2H, J = 7.35 Hz); 3.84 (s, 2H); 3.34 (s, 2H); 1.21 (t, J=7.35 Hz, 3H)

^{13}C NMR (75 MHz, DMSO-d_6): δ 14.12 (C11); 46.63 (C8); 49.01 (C7); 60.12 (C10); 114.51 (C2); 117.39 (C4); 121.65 (C6); 129.0 (C3); 131.46 (C5); 148.40 (C1); 172.34 (C9)

UV: 210 nm (Σ = 38378 M^{-1} cm^{-1}); 251 nm (Σ = 13254 M^{-1} cm^{-1}); 307 nm (Σ = 3368 M^{-1} cm^{-1})

MS: 277 (M^+); 176 (M^+ -$C_4H_9NO_2$); 116 (M^+ - $C_6H_4NCl_2$)

IR (KBr dispersion): 3420 cm^{-1}, 3300 (NH); 1730 (C=O); 1620 (NH); 1190 (C-O)

Preparation of 5,6-dichloro-3,4-dihydro-1(1H)iminoquinazoline-3 acetate hydrobromide (II)

Ethyl N-(6-amino-2,3-dichlorobenzyl)glycine was dissolved in 4 parts of toluene. A solution of cyanogen bromide (1.1 equivalent) in 4 parts of toluene was then added while maintaining the reaction mixture temperature below 30°C. The reaction mixture was heated to reflux for 1 hour. The mixture was cooled to 0-5°C and stirred at 0-5°C for 1 hour. The mixture was filtered and the solids were rinsed

with toluene (2 X 1 part). The solids were dried at 50°C in a high vacuum oven overnight to give Compound II in 96-98% yield.

^{1}H NMR (300 MHz, DMSO-d$_6$): δ 7.57 (d, 1H, J = 8.5 Hz); 7.05 (d, 1H, J = 8.5 Hz); 4.67 (S, 2H); 4.55 (S, 2H); 4.19 (q, 2H, J = 7.0 Hz); 1.25 (t, 3H, J = 7.0 Hz)

^{13}C NMR (75 MHz, DMSO-d$_6$): δ 14.15; 48.07; 50.46; 61.80; 115.05; 118.42; 126.22; 128.19; 129; 130.16; 132.92; 167.09

UV: 217nm (Σ = 40337 $M^{-1}cm^{-1}$-); 262 nm (Σ = 18961 $M^{-1}cm^{-1}$)MS: 302 (M^+-HBr); 256 (M^+-C_2H_7OBr)

IR: (KBr dispersion): 3200 cm^{-1}; 1740 (C=O); 1666 (C=N); 1200 (C-O).

Preparation of 6,7-Dichloro-1,5-dihydroimidazo[2,1-b]quinazolin-2(3H)-one (III)

5,6-dichloro-3,4-dihydro-2(1H)iminoquinazoline-3-acetate HBR (compound II) was suspended in 46 parts water. TEA (1.5 equiv.) was added in one portion, and the mixture stirred for 2 hours. The solution was filtered, and the filter cake washed with water (2 x 3 parts). The solids were suspended in ethanol (20 parts) and stirred for 4 hours. The solution was filtered. The solids were rinsed with ethanol (2 x 2/3 parts), and dried at 40°C in a high vacuum oven overnight to give compound III in 86 to 88% yield.

Melting point: 338 - 341°C

^{1}H NMR (300 MHz, DMSO-d_6, TFA-d_1); δ 13 (br s, NH); 7.15 (d, 1H, J = 8.7 Hz, C(3)-H); 7.12 (d, 1H, J = 8.7 Hz, C(2)-H); 4.71 (s, 2H, C(7)-H_2); 4.29 (s, 2H, C(8)-H_2)

^{13}C NMR (75 MHz, DMSO-d_6, TFA-d_1): δ 44.01 (C7); 52.56 (C8); 117.10 (C2); 127.92 (C4); 129.58 (C6); 130.52 (C3); 132.11 (C5); 153.28 (C1); 171.34 (C9)

UV: 210 nm (Σ = 18772 M^{-1} cm^{-1}); 255 nm (Σ = 22708 M^{-1} cm^{-1})

MS: 256 (M^+); 221 (M - Cl)

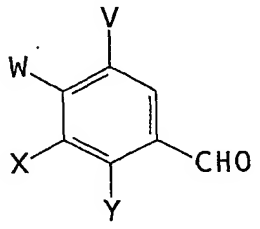
IR (KBr dispersion): 3010, 3000, 1700 (C=O), 1630 (C=N), 1562, 1468, 1437 (C=C), 1197, 1187 cm^{-1}

While the present invention has been particularly described, in conjunction with a specific preferred embodiment, it is evident that many alternatives, modifications and variations will be apparent to those skilled in the art in light of the foregoing description. It is therefore contemplated that the appended claims will embrace any such alternatives, modifications and variations as falling within the true scope and spirit of the present invention.

Thus, having described the invention, what is claimed is:

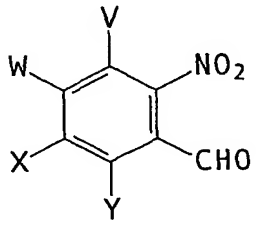
1. A method for making a 6,7-dihalo-1,5-dihydroimidazo[2,1-b]quinazolin-2(3H)-one of formula (III) from a 2,3-dihalobenzaldehyde of formula (IX) comprising the steps:

(a) nitrating a compound of formula (IX):



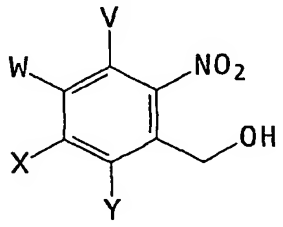
(IX)

to form a compound of formula (X):



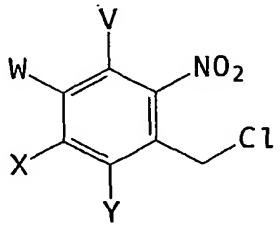
(X)

(b) reacting the compound of formula (X) under reducing conditions to form a compound of formula (XI):



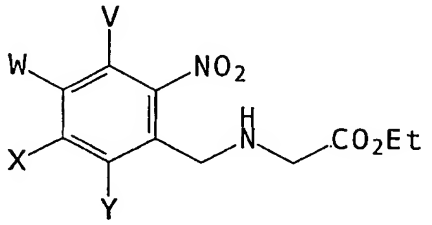
(XI)

(c) reacting the compound of formula (XI) under chlorination conditions to form a compound of formula (VIII):



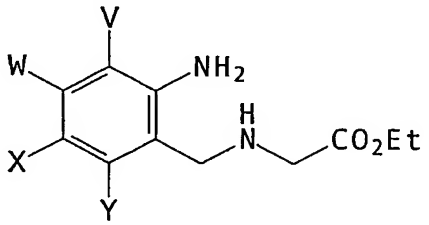
(VIII)

(d) reacting the compound of formula (VIII) under alkylation conditions to form a compound of formula (VI):



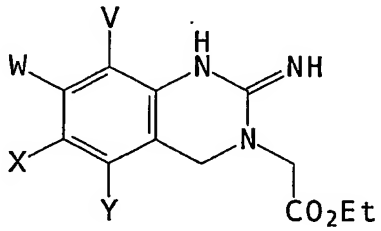
(VI)

(e) reacting the compound of formula (VI) under reducing conditions to form a compound of formula (I):



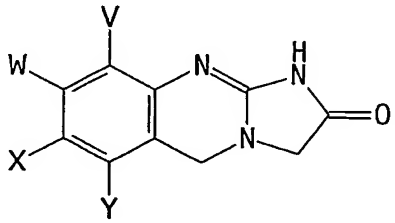
(I)

(f) reacting the compound of formula (I) under bromocyanation conditions to form a compound of formula (II):



(II)

(g) reacting the compound of formula (II) under cycloalkylation conditions to form the compound of formula (III):



(III)

(wherein X and Y are independently selected from the group comprising F, Cl, Br and I; and V and W are independently selected from the group comprising H, F, Cl, Br and I).

2. A method for reducing an ethyl N-(2,3-dihalo-6-nitrobenzyl) glycine of formula (VI) as defined in claim 1 to form an ethyl N-(6-amino-2,3 dihalobenzyl) glycine of formula (I) as defined in claim 1 comprising the steps of:

forming a suspension of said ethyl N-(2,3-dihalo-6-nitrobenzyl) glycine in concentrated HCl;

forming a mixture of stannous chloride in concentrated HCl;

adding the glycine suspension to the stannous solution at an elevated temperature;

filtering the solids and dissolving the solids in water and an organic solvent;

adjusting the pH of the solution to an alkaline pH;

separating the organic phase and extracting the aqueous phase with an organic solvent;

combining the organic phases and concentrating the solution to precipitate the solids; and

collecting the solids as the said ethyl N-(6-amino-2,3-dihalobenzyl) glycine of formula (I).

3. A method for reducing an ethyl N-(2,3-dihalo-6-nitrobenzyl) glycine of formula (VI) as defined in claim 1 to form an ethyl N-(6-amino-2,3 dihalobenzyl) glycine

of formula (I) as defined in claim 1 comprising the steps of:

forming a solution of said ethyl-N-(2,3-dihalo-6-nitrobenzyl) glycine of formula (VI) in water and an organic solvent;

mixing the solution with a sulfided platinum on carbon catalyst under hydrogen pressure;

removing the catalyst;

concentrating the filtrate;

diluting the concentrate with water and an organic solvent and adjusting the pH to alkaline;

separating the organic phase;

concentrating the organic phase; and

recrystallizing the said ethyl N-(6-amino-2,3-dihalobenzyl) glycine of formula (I) from the organic phase.

4. A method for the cyclization of a 5,6-dihalo-3,4-dihydro-2(1H)iminoquinazoline-3-acetate HBr of formula (II) as defined in claim 1 to form a 6,7-dihalo-1,5-dihydroimidazo[2,1-*b*]-quinazolin-2(3H)-one of formula (III) as defined in claim 1 comprising the steps of:

suspending the iminoquinazoline salt in water;

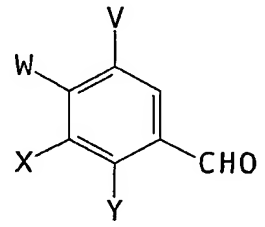
adding an organic base to the suspension and mixing; and

separating and drying the solids to form the said 6,7-dihalo-1,5-dihydroimidazo[2,1-*b*]-quinazolin-2(3H)-one of

formula (III).

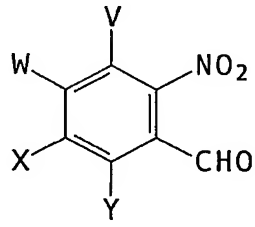
5. A method for making an ethyl N-(2,3-dihalo-6-nitrobenzyl)glycine of formula (VI) as defined in claim 1 from a 2,3-dihalobenzaldehyde of formula (IX) as defined in claim 1 comprising the steps:

nitrating the compound of formula (IX):



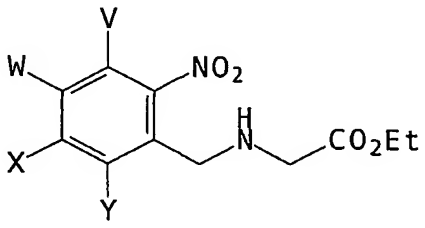
(IX)

to form a compound of formula (X) as defined in claim 1:



(X)

reacting the compound of formula (X) under reductive amination conditions to form the said compound of formula (VI):



(VI)

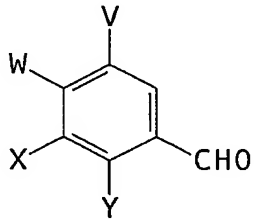
6. The method of claim 5 wherein the nitration is performed by dissolving the compound of formula (IX) in sulfuric acid and then adding nitric acid to the solution.

7. The method of claim 6 wherein the reductive amination is performed by dissolving the compound of formula (X) in alcohol, neutralizing with an organic base and then reducing.

8. The method of claim 7 wherein the organic base is triethylamine and the reducing agent is sodium cyanoborohydride.

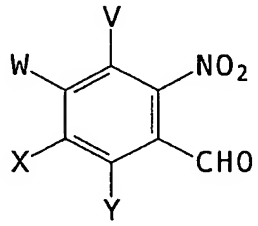
9. A method for making a 2,3-dihalo-6-nitrobenzyl chloride of formula (VIII) as defined in claim 1 from a 2,3-dihalobenzaldehyde of formula (IX) as defined in claim 1 comprising the steps:

(a) nitrating the compound of formula (IX):



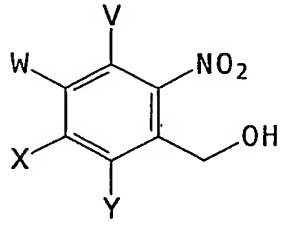
(IX)

to form a compound of formula (X) as defined in claim 1:



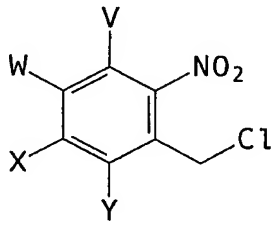
(X)

(b) reacting the compound of formula (X) under reducing conditions to form a compound of formula (XI) as defined in claim 1:



(XI)

(c) reacting the compound of formula (XI) under chlorination conditions to form the compound of formula (VIII):



(VIII)

10. A method as claimed in any preceding claim wherein V and W are both H.

11. A method as claimed in any preceding claim wherein X and Y are both Cl.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(81) Designated States *(national)*: AE, AG, AL, AM, AT (utility model), AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ (utility model), CZ, DE (utility model), DE, DK (utility model), DK, DM, DZ, EC, EE (utility model), EE, ES, FI (utility model), FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK (utility model), SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 02/008228 A3

(54) Title: METHOD FOR THE MANUFACTURE OF ANAGRELIDE

(57) Abstract: Methods are provided for making certain 6,7-dihaol-1,5-dihydroimidazo [2,1-b]quinazolin-2(3H)-ones from 2,3-dihalobenzaldehydes. A method is also provided for making the intermediate ethyl N-(2,3-dihalo-6-nitrobenzyl)glycines from 2,3-dihalobenzaldehydes and for reducing the glycine compounds using either $SnCl_2$ or a specially defined catalyst. A cyclization method to form the desired 6,7-dihalo-1,5-dihydroimidazo[2,1-b]quinazolin-2(3H)-ones from the corresponding iminquinazoline compounds is further provided. These methods are particularly suitable in the manufacture of Anagrelide base.

INTERNATIONAL SEARCH REPORT

Int nal Application No
PCT/GB 01/03362

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D487/04 C07C209/36 C07C209/08 C07C201/08 C07C201/12
C07C201/14 //(C07D487/04,239:00,235:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 4 146 718 A (JENKS THOMAS A ET AL) 27 March 1979 (1979-03-27) cited in the application columns 7, 8, reaction scheme B column 3, line 45 -column 4, line 9 abstract	1,5,9
X	column 6, line 8 - line 30; examples 2-4	2,4,10, 11

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X	example 1	3,10,11

	-/--	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
17 May 2002	27/05/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Hass, C

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INTERNATIONAL SEARCH REPORT

Int· ›nal Application No
PCT/GB 01/03362

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	US 5 801 245 A (LANG PHILIP C) 1 September 1998 (1998-09-01) cited in the application column 3; claims 1,2; example 1	1-6,9-11
A	US 5 391 737 A (REITER JOZSEF ET AL) 21 February 1995 (1995-02-21) abstract	1,10,11
A	EP 0 021 338 A (HOFFMANN LA ROCHE) 7 January 1981 (1981-01-07) page 1, line 20 page 3, line 20 -page 4, line 31	1,10,11
A	US 4 208 521 A (CRENSHAW RONNIE R ET AL) 17 June 1980 (1980-06-17) cited in the application claim 1	1
A	DE 28 32 138 A (HOFFMANN LA ROCHE) 8 February 1979 (1979-02-08) claim 1	1
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Int nal Application No
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INTERNATIONAL SEARCH REPORT

Information on patent family members

Int[illegible]al Application No
PCT/GB 01/03362

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